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APHRODISIAC DRUGS FOR WOMEN AND ITS CORRELATION WITH SEROTONIN

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ABSTRACT: Effect of PGE_1 (0.4 mg/kg i p) and Drugs affecting serotonin and Prostaglandin metabolism including aphrodisiac plants on the serotonin level in rat uterus in estrus, and pregnant state were taken up in the present study. Female aphrodisiac an upcoming branch became a thrust area after the discovery of Sildenfil. Some known aphrodisiac plants and natural products showed to increase uterine 5-HT level. The 5-HT response in rat's uterus is different in estrus and non-estrus state .The uterine 5-HT content increase three fold in estrus in comparison to non-estrus state. Drugs like l-tryptophan increase 5-HT synthesis and projected 5-HT concentration in uterine tissue. Monoamine oxidase inhibitor (MAOI) pargyline also increased uterine tissue 5-HT. PGE_1 like brain and intestine increased in uterine 5-HT. Indomethacin and diclofenac sodium known to block prostaglandin synthesis by inhibiting prostaglandin synthetase like pCPA reduced the 5-HT content. In pregnant uterus 5-HT content increased while Prostaglandin treatment both in estrus and non-estrus condition also increased 5-HT content more than three fold. Herbs with known aphrodisiac activity contain 5-HT showed significant increase in uterine 5-HT content significantly. The results such obtained show a silvelining in future study of these drugs for therapeutic use.

Key word: Female aphrodisiac, Herbal aphrodisiac, 5-HT.

INTRODUCTION

India bears a longstanding Medicare system with rich heritage evolved on a continuous process of experience- based scientific research. Silajit a mountain exuded was under use as to vitalize, loaded with gold and other minerals. To change gold into fine powder for consumption as rejuvenator by Amla also known as gold making juice. In the later period, an initial form of chemistry together with

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philosophical and magical association the Alchemy appeared. (Mehedihasan 2002).

Studies on a female aphrodisiac an upcoming branch needs attention to increase the state of arousal. In order to accomplish these phenomena, a substance or activity would require impacting the libido in women. While in age old, Ayurveda dating back to 5000 years deals with the rejuvenating drugs in Vajikarana specialty (Debnath 2002) may be nomenclature as aphrodisiac with detail description for males(Charaka Samhita, chi 2). On evaluation the food and natural products described as aphrodisiac (vajikaran) known to have serotonin content.

Serotonin plays an important role in sex cycle but its involvement in the aphrodisiac activity leading to orgasm is not fully elucidated. Some known aphrodisiac plants and natural products showed to increase uterine 5-HT effect and so also increases uterine 5-HT level. Yohimbe is also popular as a female aphrodisiac that increases sexual desire in women having low sex drive (Meston *et al.* 1996).

Serotonin is widely distributed biogenic amine present in animal and plant kingdom with complete synthesizing and degradation enzyme system and stored, in the tissue, being synthesized for specific function (Fozard 1989). Serotonin's role in the majority of peripheral processes is similar in males and females. The female genital tract is innervated by the pelvic splanchnic, hypogastric and pudendal nerves (Grey 1966) In women, contractions in the smooth muscles of the genital organs entail orgasm, which are characterized by rhythmic, synchronized vaginal, anal and uterine contraction (Bohlen *et al.* 1982, Fox 1976)

One of the primary functions of peripheral serotonin is the regulation of vascular tone and blood flow (Meston *et al.* 1996). Serotonin administration produces contractions in the rat and human uterus (Wrigglesworth 1983) The 5-HT antagonists and ketaserine inhibits 5-HT induced contractions of the rat uterus *in vitro.* Serotonin produced contractions in human myometrial smooth muscle obtained from cesarean section. The contractile effect of 5-HT in genital tissues as agent is more potent than noradrenalin, prostaglandins $F_{2\alpha}$ and E_2 (Maigaard *et al.* 1986).

Similarly prostaglandins are also a strong contender to designate important transmitters in parturition and labour like 5-HT(Acharya *et al.* 1989) .In our earlier studies, we has postulated interrelationship of PGs and 5-HT in brain and GIT (Debnath *et al.* 1978). In uterine tissue, existence of such correlation is questionable. To substantiate the role of male aphrodisiac drugs on uterine tissue 5-HT and to correlate with female aphrodisiac activity are essential. In Ayurveda, drugs with aphrodisiac (vajikarana) initiator were known for their use especially in males but not for females.

The physiological changes that occurs in different female reproductive organs were first recorded by Sintchak and Geer in 1975 photo plethysmo graphically with introduction of a probe to record the vaginal blood flow. That was the first practical and reliable measurement device for vaginal blood flow recording . This evidence drawn attention to the scientists as the starting point to record physiological changes with evidence before the role of aphrodisiac on female to yield orgasm was less known. Research in late 1970s and early 1980s had provided ample information about the female sex physiology. The psycho physiological assessment of female sexual function has relatively short history in sexology (Rosen and Beck 1988). In post Sildenafil era, attempts are being made to search for a suitable replica for

female aphrodisiac with limited success (Terrett *et al.* 1996) . The incidence of female sexual dysfunction including libido is of great concern not only in India but also in abroad. The female sexual arousal is associated with neurotransmitter mediated vascular smooth muscle relaxation, which stimulate vaginal lubrication, vaginal wall engorgement and increased clitoral vaso-congestion. Thus, women with atherosclerotic vascular disease experience decrease response of vascular smooth muscle relaxation and orgasm (Park and Colleagues 1997).

Different reproductive functioning centers concerning infertility mainly focus in and around ovarian function and general gynecological health issues concentrating on the reproductive potential of a male. Knowing full well female sexual dysfunction but the sexual implications *per se* is hardly addressed. In the present study effect of 5-HT synthesis and metabolizing drugs along with some rejuvenating and aphrodisiac drugs are evaluated on serotonin content in rat uterus in different condition explore female aphrodisiac.

MATERIALS AND METHODS

The study was conducted on female Wistar albino rats (120-150 g). The rats were maintained on standard Hind Lever diet and were housed in an air cooled room (25^{O}C) in colony cages. Animals were fasted overnight but water was allowed *ad lib*. before experimentation. Different drugs were administered at different times shown in Table 1 and rats were killed by decapitation between 9 and 11 am to take out uterine tissue in frozen condition. Uterine tissue serotonin was estimated by the method of Snyder *et al.* (1965) in non-estrus and estrus state. Artificial estrus was produced by injection of stilbesterol, described in detail (Debnath 1977) . Statistical analysis of data was done by Student's 't' test.

The choice of the dose and route of administration was based on earlier reports (Debnath *et al.* 1978, Bhattacharya *et al.* 1975 & 1976). All the drugs were purchased from Sigma except PGE_1 gifted by The Upjohn Company, USA. The study protocol was approved by Institutional Animal Ethics Committee.

RESULTS AND DISCUSSION

The response of 5-HT in rat's uterus is different in estrus and non-estrus state .The uterine 5-HT content increase three fold in estrus in comparison to non-estrus state. Drugs like l-tryptophan precursor amino acid pre-treatment increase 5-HT synthesis and projected 5-HT concentration in uterine tissue. Monoamine oxidase inhibitor (MAOI) pargyline block the degradation of 5-HT to 5-HIAA also increased uterine 5-HT. PGE_1 increased uterine 5-HT like brain and intestine. Indomethacin and diclofenac sodium known to block prostaglandin synthesis by inhibiting prostaglandin synthetase like pCPA reduced the 5-HT content. In pregnant uterus 5-HT content increased while Prostaglandin treatment both in estrus and non-estrus condition also increased 5-HT content more than three fold. Herbs with known aphrodisiac activity contain 5-HT which showed significant increase in uterine 5-HT content significantly. The results are summarized in Table 1.

In the present study 5-HT content in rats uterine tissue showed changes depending upon the synthesis and degradation enzyme acting drug response similar to GIT and brain. The prostaglandin E_1 increased 5-HT level in uterus. Moreover, increased the 5-HT synthesis in brain, peripheral tissue and stomach established interrelationship of PGE_1 and 5-HT (Debnath

et al. 1978). Prostaglandin relationship further strengthens on the effect of indomethacin, PGE_1 increased 5-HT synthesis rate while indomethacin decreased the synthesis rate point towards further involvement of PGE_1 in 5-HT

female aphrodisiacs are not well proven. Many have supporting clinical studies showing that the hormones or chemical properties in them could actually generate positive results. In the present study aphrodisiac drugs were employed

Table 1: Effect of PGE1 (0.4 mg/kg i p) and Drugs affecting serotonin and Prostaglandin metabolism including Aphrodisiac plants on the serotonin level in Rat Uterus.

Treatment	Dose mg x day	n	5-HT concentration mcg/g wet tissue
Control (non-estrus)	-	15	1.24 ± 0.12*
pCPA	300 x 3	6	0.60 ± 0.09*
Indomethacin	25	5	0.69 ± 0.13*
Diclofenac sodium	1	5	0.34 ± 0.23*
l-Tryptophan	400	5	1.99 ± 0.21*
Pargyline	75	6	2.05 ± 0.19*
PGE_1	0.4	5	2.18 ± 0.25*
Pregnancy	-	5	1.42 ± 0.11
Control (Estrus)	-	5	3.81 ± 0.34*
Estrus + PGE_1	0.4	4	8.76 ± 0.34*
Aswagandha	500 x 3	6	1.94 ± 0.31*
Satavari	500 x3	8	1.98 ± 0.34*
Atmagupta	500 x3	8	2.12 ± 0.23*
Banana	500 x3	8	2.43 ± 0.23*

Values are Mean ± S E, n= sample size , p< 0.01

response. It is well known that indomethacin, aspirin are being used clinically in the pregnancy for threatened abortion (Acharya *et al.* 1989, Debnath *et al.* 1994) Aphrodisiac drugs used usually for males also showed increased 5-HT in uterine tissue in rats.

Aphrodisiacs typically magical substance contains chemical properties or involves activities that stimulate hormonal responses to achieve this task. A female aphrodisiac, to work, needs to increase the state of arousal would also need to impact the libido in women. Natural

Withania somnifera, Asperagus recemosus, Mucuna prurians and *Musa paradisiac* (vegetable banana). All of them showed increased uterine 5-HT in comparison to control non-oestrus rats. There are reports that besides those drugs *Crocus sativa, Glyceriza glabra,* black tea or *Camellia senesis, Tribulus teristics* showed aphrodisiac activity (Dutta *et al.* 2002, Gupta and Shaw 2011).

In Sri Lankan traditional medicine black tea brew (BTB) of *Camellia sinensis* is claimed to have male sexual stimulant activity. Although

this claim is not scientifically tested and proven, (Ratnasooriya and Fernando 2008) Another natural herbal aphrodisiac *Withania Somnifera* (Ashwagandha), an herbal miracle that works mainly on the reproductive and nervous systems as a sexual and an energy tonic with a rejuvenating effect increases brain 5-HT. Herbal drug preparation containing Aswagandha, Satavari, Gokshura increase brain 5-HT, melatonin and histamine (Upadhyay *et al.* 1988). Withania *somnifera* reduces increases the blood sugar level, reduces glucose tolerance, impairs cognitive performance, triggers gastric ulceration, suppresses immunity, reduces libido and stimulates corticosterone secretion and exhibiting anti-stress effect in chronically stressed rats. (Bhattacharya and Muruganandam 2003).

Tribulus can be helpful for menopause, decreased libido or sex drive, impotence and male and female infertility. *Tribulus terristis* increase brain 5-HT and improve sexual dysfunction in men and women due to an increase up-regulating androgen receptor expression and nitrogen oxide synthetase neurons in the regions of the brain that regulate sexual behavior and desire function (Kerry and Lovell 2001).

Myristica fragrance (Nutmeg) natural herbal aphrodisiac effect widely used to improve the natural aroma and flavor of food (Sonavane *et al.* 2001). *Asparagus racemosus* is used as a nutritive tonic, natural herbal aphrodisiac, and as an, galactogue, and also used as antispasmodic and in epilepsy, depression and hysteria. Shatavari roots promote breast milk production and are used to treat low sex drive and infertility and decrease the menopausal symptoms by the improvement in vaginal dryness associated with menopause (Dutta *et al.* 2002). *M. pruriens* is widely used as male and female aphrodisiac. Recent study reveals that *M. pruriens* showed antimicrobial activity (against gram positive, gram negative and spore forming bacteria and also fungi) on the methanol leaf extract and 5-HT was detected in the seed (Salau 2007).

The effect of *Crocus sativus* (saffron) was studied on male erectile dysfunction(ED). It is presumed that *Crocus sativus* may replace phosphodiesterase 5-inhibitors as aphrodisiac (Ali *et al*. 2009). Aphrodisiac activity of *Glycyrrhiza glabra* in male Wistar rats exhibiting the greatest efficacy in delaying ejaculation like re-uptake inhibitors (SSRIs) .The brain area most associated with sexual behavior is the limbic system. Indicates a relationship between brain dopamine, 5-HT and sexual behavior (Singh and Mukherjee 1968) Both dopamine and 5-HT are implicated in depression are known to effect libido, erection, ejaculation and orgasm. It is also suspected that monoamines play a crucial role in the regulation of sexual behavior (Sudhir *et al.* 2012).

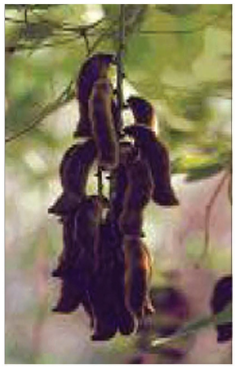
Vegetable banana contain 5-HT and proved to have antiulcer effect. Ethanol extract of banana (BE) was reported to increase the accumulation of eicosonoids like prostaglandin E and I_2 (PGE and PGI_2) and leukotrienes B_4, and C_4/ D_4 (LTB_4, C_4/ D_4) in the human gastric and colonic mucosal incubates.(Goel *et al*. 1989, Travares *et al.* 1990, Goel and Maity 1992). Aqueous extracts of onion, garlic and ginger on platelet aggregation and metabolism of arachidonic acid in the blood vascular system are known (Srivastava 1984).

Research on the relationship between aphrodisiac effect of herbal drugs in female and correlation with serotonin and sexual functioning has focused primarily on Central Nervous System (CNS) activity. In animal experiments, to evaluate the mechanism directly

drug could be injected into the CNS, or into the periphery and subsequently examine sexual responding to map relationship between sexual activity and specific serotonin receptor activity in serotonin rich brain regions. In human, such direct examination for ethical reasons cannot be conducted. Only possible to depends on the indirect research to link between serotonin and sexual behavior that too focused primarily on centrally mediated events. Antidepressant, anti-psychotic, or other serotonergic drugs have been discussed almost exclusively in terms of serotonin receptor subtype activation or inhibition in the CNS. Clearly, serotonin may mediate some aspects of sexual functioning almost entirely within CNS. Evidence suggests that hypothalamic serotonin activity can produce lordosis response in rats (Uphouse *et al.* 1996). However, the vast majority of serotonin receptors are located in the periphery of the body, with only 5% in the CNS (Prichard and Smith 1990) Particular artery may constrict or dilate when exposed to serotonin depending upon whether it was relaxed or constricted prior to serotonin exposure (Yang and Mehta 1994). Serotonin may also act synergistically with other substances to affect vasoconstriction or dilatation(Yildiz *et al.* 1998).

Sexual difficulties often accompany certain disorders that are characterized by abnormalities in peripheral serotonin. It is possible that these sexual difficulties result at least in part, from deregulation. For example, depression, which has been traditionally viewed as a psychological disease, is characterized by changes in sexual functioning and the evidences suggests that peripheral serotonin as measured by platelet serotonin level, is lower in depressed individuals as compared to non-depressed (Takahashi 1976). Platelet serotonin levels may be inversely related to severity of depression (Mann *et al.* 1992)

A PHRODISIAC PLANTS



Mucuna prurians (Allkushi)

Withania somnifera (Ashwagandha)

Asperagus recemosus (Satamuli)

Musa paradisia (Banana)

Tribulus terristis (Ghoshura)

Myristica Fragrans Houtt (Zaifal)

Adrenergic stimulation has been reported to produce an increased release of 5-HT from the enterochromaffin cells of the gastrointestinal tract and in women(Ahlman *et al*. 1976), adrenergic activity facilitate sexual arousal (Menston & Gorzalka 1996). It is feasible that increased adrenergic activity during sexual stimulation in women produces an acute increase in 5-HT. In myometrial preparations, Prostaglandin $F_2\alpha$ ($PGF_2\alpha$), Prostaglandin E_2 (PGE_2), Noradrenaline (NA) and Serotonin (5-HT) all caused concentration-related contractions (Miaigaard *et al*. 1986), while oxytocic activity of both 5-HT and PGs was reported in rats (Acharya *et al.* 1985).

Premature ejaculation (PE), whose pathophysiology is still not clearly identified, is the most common male sexual dysfunction, yet it remains under diagnosed and undertreated. Pharmacologic manipulation of the serotonergic system has been performed in rats, with the selective serotonin mediated antidepressant (Giuliano *et al.* 2006). Retrospective analysis of the data indicated that fibers may be more sensitive to uterine stimulation when rats are in vaginal estrus/proestrus than in diestrus/ metestrus. The hypothesis of an implication of brain 5-HT in the mechanism of psychogenic sexual deficiency and the possibility of a therapeutic approach with drugs interfering with 5-HT turnover (Debnath *et al.* 1978) may be rational to improve female sexual dysfunction.

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